UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,557	10/31/2003	Samuel Jotham Reich	129402.00801	7768

21269 7590 09/03/2008

PEPPER HAMILTON LLP
ONE MELLON CENTER, 50TH FLOOR
500 GRANT STREET
PITTSBURGH, PA 15219

EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,557	REICH ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-39,41,46-62 and 64-77* is/are pending in the application.

4a) Of the above claim(s) *46,51,52,55,56,58-60,64,65,68,69,71,74 and 77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-39, 41, 47-50, 53, 54, 57, 61, 62, 66, 67, 70, 72, 73, 75, and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Official Action is made in response to applicants papers filed 5/27/08. Applicant has amended the claims such that the invention is drawn to a method of inhibiting HIF-1alpha via an siRNA targeting a region defined by SEQ ID NO: 223.

Any rejections of record made in the previous Action and not repeated below are withdrawn.

Applicants arguments filed 12/03/07 have been considered but are moot in view of the amendments made and the new grounds of rejection below. The new grounds of rejection made below to show that Thrue et al do indeed teach targeting a region of HIF-1alpha defined by SEQ ID NO: 22. The rejection below relies on only the disclosure in Thrue et al that is supported by the priority document US Provisional 60/370,126.

Claims 33-39, 41, 53-54, 57, 61, 62, 66, 67, 70, 72, 73, 75, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thrue et al [US 2004/0096848], in view of Robinson et al [5,801,156] and Tuschl et al [US 2004/0259247].

The invention is as stated in the rejected claims.

Thrue et al have taught oligomeric compounds for the modulation of HIF-1alpha [HIF-1].[The examiner will point to support in the priority document US 60/370126 for

clarity] It has been taught at pages 1 and 2, for example that "It has been demonstrated that engineered down-regulation of HIF-1.alpha. by intratumoral gene transfer of an antisense HIF-1.alpha. plasmid leads to the down-regulation of VEGF, and decreased tumor microvessel density . . ." It has therefore been taught that inhibition of HIF-1 inhibits VEGF. At page 1 it is also taught the association of HIF-1 to angiogenesis in response to hypoxic conditions.

At pages 3-4 it has been taught that the compounds of Thrue et al can be used to inhibit expression of HIF-1 in the treatment of cancers or other diseases associated with HIF-1 expression. At pages 1-3 it is disclosed that the prior art has used various antisense inhibitors of HIF-1. At pages 10 and 11 it has been taught various nucleic acid inhibitors can be used such as ribozymes, aptamers, external guide sequences oligozymes, other short catalytic RNAs or catalytic oligonucleotides, and antisense. This disclosure shows that one in the art has many different nucleic acid drugs at their disposal. The disclosed nucleic acid drugs belong to a genus of nucleic acid inhibitors where each functions in different ways where each has its benefits and drawbacks.

For example, when a new inhibitory nucleic acid compound, such as siRNA is developed, it would have been be obvious to use it since it too belongs in the genus of inhibitory nucleic acid drugs all used for the same purpose, inhibiting a target gene sequence.

At page 21 it is taught to use various moieties or conjugates to enhance activity, cellular distribution or cellular uptake of oligonucleotides.

On page 11 it is also disclosed conjugates such as ibuprofen were well known at the time of invention.

At page 25 it is taught that it was known at the time of invention to formulate oligonucleotides for ophthalmic or other pharmaceutical purposes/administration. Also on page 25 liposomes are taught as one of many well known means for delivering oligonucleotides for therapeutic purposes..

Thrue et al have therefor taught that HIF-1 can be targeted by various oligonucleotide inhibitors in the treatment of diseases associated with HIF-1 including conditions were VEGF inhibition would be desirable.

Thrue et al also teach an antisense oligonucleotide that targets within the recited SEQ ID NO: 223. SEQ ID NO: 3 of Thrue et al is an antisense that corresponds to nucleotides 5-20 of SEQ ID NO: 223. Thrue et al have therefore shown that the target region defined by SEQ ID NO: 223 was known to be an accessible region for nucleic acid hybridization inhibitors.

Robinson et al have taught that age-related macular degeneration as well as many other neovascular diseases of the eye can be treated with VEGF antisense compounds. Since it was known in the art that the inhibition of HIF-1alpha also inhibits VEGF activity it would have been apparent and obvious to one or ordinary skill in the art that HIF-1alpha is also a viable target to treat age related macular degeneration, especially since Thrue et al have taught the inhibition of angiogenesis with HIF-1alpha LNAs, for example. Also one in the art would have known to use any of the available nucleic acid inhibitors known in the art for inhibiting a target gene.

Tuschl et al have taught siRNA as inhibitors of nucleic acid targets in mammalian cells and have taught the size range 19-25 as a standard siRNA size range, see paragraph [0009], for example. Tuschl et al describe another nucleic acid inhibitor developed after the teachings of Robinson and at the time of Thrue et al. siRNA is therefore one of the several available nucleic acid based inhibitor available to one in the art at the time of invention. Tuschl et al teach that siRNA can be used to inhibit any desired target gene in mammalian cells and in humans. At paragraph [0008] it is taught that the agents of the invention [siRNA] are capable of mediating target specific RNA interference or other target specific nucleic acid modifications such as DNA methylation, said agents having an improved efficacy and safety compared to prior art agents. It appears that one in the art at the time of invention would be led to use siRNA in place of other known nucleic acid based inhibitors since siRNA is taught to possess improved safety and efficacy over the compound taught by Thrue et al and Robinson et al, for example.

Since the treatment of diseases such as retinoblastoma and other neovascular diseases or conditions with siRNA were known in the art and since the art has taught all of the limitations of the claimed invention such that one in the art is clearly brought to the claimed invention one would clearly have combined the Thrue et al disclosure to include a specified size range of siRNA and further would have known to target another neovascular disease such as age related macular degeneration. One in the art would also have known to use combinations of cancer treating compounds since combination treatments for cancers have been routinely used in the art. The invention appears to be

based on using a different, yet known compound to treat a known disease. The prior art has taught that the compound is a member of the same genus of nucleic acid inhibitors that inhibit targeted nucleic acids. The prior art has taught to target the genes targeted in the instant invention with other members of the nucleic acid inhibitory compounds.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thrue et al [US 2004/0096848], in view of Robinson et al [5,801,156] and Tuschl et al [US 2004/0259247] as applied above, and further in view of Tuschl, T. [Nature Biotechnology Vol. 20:446-448, 5/2002] and Noonberg et al [US5,624,803].

The invention is as above but where the siRNA is expressed from an viral [AAV] vector.

Tuschl has taught the expression of siRNA from vectors and asserts that the endogenous expression of siRNAs from vectors is thought to overcome some limitations of exogenous siRNA delivery. Tuschl asserts that the use of viral vectors can be advantageous for use in cells refractory to plasmid vectors, for example. The use of vectors to express small RNAs is not new. Noonberg et al have taught for example in vivo nucleotide generators to produce small RNAs in mammals, for example (see claims, for example). It is noted that instant specification appears to admit that it would be routine to select vectors to express siRNA and cites several references at pages 13

and 14 and further at pages 14 –15 there is specific reference to several citations that teach AAV vectors, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

/Sean R McGarry/
Primary Examiner, Art Unit 1635